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Deleuran, Thomas; Schmidt, Morten; Vilstrup, Hendrik; Jepsen, Peter

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DR. THOMAS DELEURAN (Orcid ID : 0000-0001-7319-975X)

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Time-dependent incidence and risk for myocardial infarction in patients with alcoholic cirrhosis

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Authors: Thomas Deleuran, MD, PhD[1, 2]; Morten Schmidt, MD, PhD, Associate professor[3-5]; Hendrik Vilstrup, MD, DSc, Professor[1]; Peter Jepsen, MD, PhD, Associate professor[1, 3]

Affiliations:

1. Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark
2. Department of Gastroenterology, Aalborg University Hospital, Aalborg, Denmark.
3. Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark
4. Department of Cardiology, Regional Hospital West Jutland, Herning, Denmark
5. Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark

Correspondence: Thomas Deleuran, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
Phone: +45 2371 5703, Fax: +45 784 62860
E-mail: thomas.deleuran@clin.au.dk

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Abstract

***Background**:* It remains unsettled whether alcoholic cirrhosis is a risk factor for myocardial infarction (MI).

***Methods**:* We used data from nationwide healthcare registries to study all Danes diagnosed with alcoholic cirrhosis in 1996–2014, and five controls were matched to each of them on gender and age. We excluded everyone with ischemic heart disease and used Cox regression to estimate the incidence rate ratio of MI adjusted for potential cardiovascular confounders. Further, we described the MI-risk with non-MI death as a competing risk.

***Results**:* We included 22,867 patients (67% men) with a median age of 57 years. During the first year of follow-up, their incidence rate ratio of MI was increased to 1.24 (95% CI: 0.94–1.62), driven by the effect among women (2.13, 95% CI: 1.17–3.87) and those with most severe cirrhosis (1.32, 95% CI: 0.91–1.90). After the first year, the overall incidence rate ratio fell to (0.89, 95% CI: 0.76–1.05). Patients were more likely to die from non-MI causes (33.7% vs. 1.0%), which protected them against MI. The overall 1-year MI-risk was similar in patients and controls: 0.38% (95% CI: 0.30–0.47%) vs. 0.34% (95% CI: 0.31–0.38%). After five years of follow-up, male patients had lower MI-risk than their controls, whereas women with cirrhosis had an increased MI-risk throughout follow-up.

***Conclusions**:* The incidence rate of MI was increased the first year following a diagnosis of alcoholic cirrhosis, in particular in women and those with most severe liver disease. Due to the competing risk of non-MI mortality, the MI-risk was not increased.

Keywords: Alcoholic cirrhosis, myocardial infarction, public health.

Introduction

Myocardial infarction (MI) is a leading cause of death worldwide.[1] In patients with cirrhosis (80% alcoholic), cross-sectional evidence from computed tomography angiographies show a high prevalence of severe coronary stenosis.[2-5] It appears that, statins reduce their mortality and rate of hepatic decompensation.[6] Moreover, MI runs a particularly grave course in these patients and they have an increased mortality due to ischemic heart disease.[7-9] On the other hand, their peripheral vasodilatation leads to a lower mean arterial pressure that might reduce cardiac strain and protect against acute coronary events.[10] These seemingly contradictory observations raise two questions: First, is cirrhosis a cause of MI? We addressed this question by comparing the incidence rate of MI between alcoholic cirrhosis patients and matched controls. Second, do cirrhosis patients experience more MIs, taking their high risk of death from other causes into account?[11] One reason for the unclear state of knowledge is that the two questions are in fact distinct and thus may have different answers. Neither has been answered before. We addressed them in an observational cohort study. We expected alcoholic cirrhosis patients to have a higher incidence rate of MI than controls, and that their actual risk of experiencing a MI is lower due to their higher risk of death from causes unrelated to MI.

Methods

Data sources

We conducted a Danish nationwide population-based matched cohort study. All the 5.6 million Danish residents have free tax-funded access to hospital care.[12] The Danish National Patient Registry (NPR) holds data on all admissions to Danish hospitals since 1977, and emergency room and outpatient visits since 1995. The data include relevant dates and discharge diagnoses coded in accordance with the International Classification of Disease edition 10 (ICD-10) from 1994, and the ICD-8 before that. Data also include surgical procedures coded in accordance with the Nordic Classification of Surgical Procedures (NCSP).[13]

The Danish Civil Registration System continuously monitors the vital status including dates of death of all Danish residents.[14] It also issues a unique personal identifier to all Danish residents at birth or immigration. This number enables unambiguous individual-level linkage between the NPR and the Danish Civil Registration System.[14]

Patients, population controls, and outcome

First, we identified all Danish residents with a first-time diagnosis of alcoholic cirrhosis (ICD-8: 571.09; ICD-10: K70.3, K70.4) in 1996–2014. Second, we defined each patient's 'index date' as the date of the first registration with the diagnosis alcoholic cirrhosis. Third, population controls from the general Danish population without alcoholic cirrhosis or unspecified cirrhosis (ICD-8: 571.92, 571.99; ICD-10: K74.6) were matched to the alcoholic cirrhosis patients 5:1 on age, gender, and birthdate. The controls were given the same index date as their corresponding patient. Fourth, we excluded alcoholic cirrhosis patients (4.8%) and controls (3.9%) with a history of ischemic heart disease before their index date (ICD-10: I20.x, I21.x, I22.x, I23.x, I24.x, and I25.x), to focus on first-time MI. Fifth, patients were subcategorized as those with and without hepatic decompensation on or before the index date. Decompensation was defined as a diagnosis for ascites (ICD–10: R18.x), gastrointestinal hemorrhage (ICD-10: I85.9, K92.x), hepatic encephalopathy (ICD–10: K70.4, K72.x), portal hypertension (K76.6), hepatorenal syndrome (ICD–10: K76.7) or a procedure code for paracentesis (NCSP: KTJA10A and KTJA10B), before or on the index date. Finally, we defined the study outcome as the time to a hospital admission with a diagnosis for MI (ICD-10: I21.x).

Statistical analysis

Alcoholic cirrhosis patients and their controls were followed from the index date to the date of their first admission for MI, death, or end of follow-up on 31 December 2014, whichever occurred first. We compared the incidence rate of MI in alcoholic cirrhosis patients vs. controls with stratified Cox regression, and estimated the hazard ratio which reflects the incidence rate ratio for MI.[15] We also adjusted for potential confounding by cardiovascular comorbidities registered in the NPR before the index date: diabetes, hypercholesterolemia, heart failure, peripheral vascular disease, atrial fibrillation or flutter, venous thromboembolism, hypertension, and obesity, and chronic obstructive pulmonary disease as a proxy indicator for smoking (diagnosis codes are listed in Table 1). We assessed whether the incidence rate ratio for MI changed over time using a plot of smoothed Schoenfeld residuals.[16] This plot showed that there were two time-periods with distinct estimates. We also estimated incidence rate ratios in subgroups defined by gender, age on the index date (≤49, 50–64, or ≥65 years), and compensated or decompensated cirrhosis.

An increased incidence rate (events divided by total follow-up time) does not necessarily predict an increased risk (the proportion of person alive at the beginning of follow-up that experience an event), since the risk also depends on the rate of competing risks, in this case death of other causes than MI ('non-MI deaths').[11] Therefore, the *risk* for myocardial becomes lower when non-MI mortality rises. To illustrate the contrast in non-MI mortality between alcoholic cirrhosis patients and controls, we computed their non-MI mortality rates. Finally, we used the cumulated incidence function with non-MI death as a competing risk to compute the risk for MI.[11]

Results

We included 22,867 patients with alcoholic cirrhosis and 107,485 matched controls; their median age was 57 years and 67% were males. The patients, in particular the males, had a higher prevalence of all cardiovascular comorbidities and of chronic obstructive pulmonary disease (Table 1). We followed the patients for a total of 79,423 years and observed 281 MIs, yielding a crude incidence rate of 3.6 (95% CI: 3.2–4.0) per 1,000 person years. Their controls

were followed for 892,310 years and experienced 3,267 MIs, corresponding to a crude incidence rate of 3.7 (95% CI: 3.5–3.8) per 1,000 person years. After adjustment for the higher prevalence of confounders among patients with alcoholic cirrhosis, the overall incidence rates were virtually identical: 0.98 (95% 0.86–1.13). However, the time plots revealed that the incidence rate for the patients with alcoholic cirrhosis was not constant: They had a higher incidence during their first year after cirrhosis diagnosis, but a lower incidence rate thereafter (Table 2 and Figure 1). We therefore divided the follow-up period into the first year with an adjusted incidence rate ratio of 1.24 (95% CI: 0.94–1.62) and the remaining follow-up with an adjusted incidence rate ratio of 0.89 (95% CI: 0.76–1.05) (Table 2 and Figure 1). The increased incidence rate of MI in the first year was driven by a markedly increased adjusted incidence rate ratio for the patients with decompensated cirrhosis of 1.32 (95% CI: 0.91–1.90) and a marked increase in women of 2.13 (95% CI: 1.17–3.87) (Table 2).

The patients with alcoholic cirrhosis had a markedly higher mortality rate from non-MI causes: 203.7 (95% CI: 200.6–206.9) per 1,000 person years vs. 14.1 (95% CI: 13.8–14.3) per 1,000 person years in the controls. This fact reduced their prospects of being alive and at risk for experiencing a MI. Thus, their 1-year risk of MI was essentially the same as that of the controls: 0.38% (95% CI: 0.30–0.47%) vs. 0.34% (95% CI: 0.31–0.38%), and their 5-year risk of MI was actually lower: 1.01% (95% CI: 0.88–1.15) vs. 1.64% (95% CI: 1.55–1.72). This difference was most evident for the oldest age group where the 5-year risk of MI was 1.51% (95 % CI: 1.17–1.91) for the patients with alcoholic cirrhosis compared with 3.33% (95% CI: 3.08–3.60) for their controls. The female patients had a higher incidence rate ratio for MI than males. At the same time, their non-MI mortality rate was lower than male patients': 175 (95% CI: 170–180) vs. 221 (95% CI: 217–225) per 1,000 person years. These differences explain why the 1-year risk of MI was higher for women with alcoholic cirrhosis than for controls: 0.33% (95% CI: 0.22–0.49) vs. 0.16 (95% CI: 0.13–0.21). They also explain why women with alcoholic cirrhosis remained at increased risk of MI throughout the follow-up (Table 2 and Figure 2).

Discussion

We demonstrated how the incidence rate and the risk of MI in patients with alcoholic cirrhosis vary over time and between genders. Our findings may explain the ambiguous past reports on

this issue,[2, 17] both regarding causality and clinical risk. The patients had an increased incidence rate of MI during the first year after they were diagnosed with alcoholic cirrhosis, most evident in women and in those with decompensated cirrhosis. Concerning the MI risk, the patients' high mortality from other causes resulted in an only slightly elevated first-year risk, and a lower 5-year risk. For the women with cirrhosis, the risk for MI remained elevated throughout follow-up.

This detailed temporal description was possible because our study's foundation in the Danish nationwide healthcare databases that enable a population-based design, precise estimates, and complete long-term follow-up.[18, 19] The registry's positive predictive value is 95% for alcoholic cirrhosis and above 90% for MI.[20, 21] Thus, misclassification is likely negligible. We controlled for confounding from demographic characteristics and the prevalence of cardiovascular risk factors. Even though these factors were most prevalent in men, we found the highest incidence rate ratio of MI for women with alcoholic cirrhosis compared with their controls. Moreover, the adjustment for these confounders in women only altered the estimate of their incidence rate ratio of MI by less than 10% (from 2.36 to 2.13).

A limitation was that data on antidiabetic, lipid-lowering, antihypertensive, and antiarrhythmic drug use were unavailable, but we do not find it plausible that our findings can be explained by a more widespread use of preventive medications in the controls. Importantly, confounding is a concern only relating to the incidence rate ratios, whereas the clinical risk estimates are unaffected by confounding, but highly influenced by death from competing risks.

We could not distinguish the effect of cirrhosis from that of alcohol itself, as a cohort of patients with non-alcoholic cirrhosis, or a cohort of patients with harmful alcohol intake without cirrhosis was unavailable. Moreover, etiologies other than alcohol are not well registered in the NPR.[22] Therefore, we cannot tell whether non-alcoholic cirrhosis or alcoholism is associated with MI in the same temporal way. Concerning other etiologies, cumulated evidence suggests that chronic hepatitis C is associated with MI[23] , in support of a relationship between liver disease and MI.

Cirrhotic cardiomyopathy is believed to be the major cardiac dysfunction in cirrhosis patients.[24] However, cirrhosis patients also have markedly worse coronary atherosclerosis than healthy individuals [3], and are at an increased risk for venous thromboembolism.[25] In addition, most of them present with ascites, variceal bleeding, hepatic encephalopathy, or infections.[26]

Such events are accompanied by systemic inflammation activation, increased sympathetic nervous tone, and increased cardiac output.[10, 27, 28] These mechanisms may exert an extraordinary energy and oxygen demand on the myocardium and explain the increased incidence rate of MI we found immediately after the cirrhosis diagnosis. Moreover, drugs for hepatic decompensation introduced later in follow-up (e.g. non-selective beta-blockers and diuretics) may contribute towards the lower MI incidence rate later in follow-up. Serial data on these factors along with data on hemodynamics, metabolic vs. excretory hepatic dysfunction, or on the hepatic venous pressure gradient might have helped us mechanistically explore our findings, but such information was unavailable to us.

As opposed to men, women with alcoholic cirrhosis had more than two times higher incidence rate of MI compared with controls during their first year of follow-up. Adjustment for confounders only lowered this ratio slightly, and this pattern supports that alcoholic cirrhosis is a cause of myocardial infarction in women alone; though the association might also be due to residual or unmeasured confounding. Nevertheless, it remains possible that alcoholic cirrhosis somehow reduces the widely discussed, but unexplained gender gap in incident MI found in the general population.[29] Of note, men with alcoholic cirrhosis have an elevated estrogen level, that increase their risk for breast cancer.[30] This hormonal disturbance might alter male cirrhosis patients' circulation towards a 'female' and less harmful cardiovascular risk profile.

Among patients with MI those with alcoholic cirrhosis have a higher mortality than other patients with MI,[9] but it is unclear whether that association is due to cardiac or hepatic causes. Therefore, our data motivate clinical research involving work-up for cardiovascular risk factors in newly diagnosed alcoholic cirrhosis patients. In addition, the clinical benefit of statins on cardiovascular outcomes among these patients could be pursued further.[6]

In conclusion, we found an increased incidence rate of MI only during the first year after a diagnosis for alcoholic cirrhosis compared with controls, in particular in those with the most severe cirrhosis and in women. These findings support alcoholic cirrhosis as a risk factor for MI. However, the patients' actual risk for experiencing a MI was reduced because of their multifold increased risk of competing non-MI deaths. The time dependence and the difference between rates and risks most likely explain the ambiguity among previous reports on MI-risk in patients with alcoholic cirrhosis.

Author contributions

Peter Jepsen and Thomas Deleuran performed the analysis and drafted the first edition of the manuscript. All authors were involved in the study design, interpreted the findings and revised the manuscript for intellectual content.

Conflicts of interest statement

The authors state no conflicts of interest and have no financial disclosures.

Table 1: Demographics and prevalence of potential confounders for patients with alcoholic cirrhosis and controls

	ICD-10 diagnosis codes	**Patients with alcoholic cirrhosis (N=22,867)**	**Controls (N=107,485)**
Median age in years (25^{th}–75^{th} quartiles)	-	57 (50–64)	57 (50–64)
Males (%)	-	15,579 (68)	72,123 (67)
Age ≤ 49 years (%)	-	5,676 (25)	27,601 (26)
Age 50–64 years (%)	-	12,109 (53)	57,283 (53)
Age ≥ 65 years (%)	-	5,082 (22)	22,601 (21)
Diabetes (%)	E10.x, E11.x	3,623 (11.5)	3,474 (3.2)
Hypercholesterolemia (%)	E78.x	695 (3.0)	2,216 (2.0)
Heart failure (%)	I50.x, I11.0, I13.0 , I13.2	907 (4.0)	904 (0.8)
Peripheral vascular disease (%)	I70.x–I74.x, I77.x	920 (4.0)	1,940 (1.8)
Atrial fibrillation (%)	I48.x	1,013 (4.4)	2,190 (2.0)
Venous thromboembolism (%)	I26.x, I80.1–I80.3	889 (3.9)	1,175 (1.1)
Arterial hypertension (%)	I10.x–I15.x	2,852 (12.5)	7,045 (6.6)
Obesity (%)	E65.x–E68.x	720 (3.2)	1,839 (1.7)
Chronic obstructive pulmonary disease (%)	J43.x–J44.x	1,747 (7.6)	2,078 (1.9)

Table 2: Incidence rates, cumulative incidence proportions (risks), adjusted incidence rate ratios for myocardial infarction among patients with alcoholic cirrhosis patients vs. controls, according to time since diagnosis and gender, age, and disease severity

	Incidence rate (95% CI) per 1,000 person years				**Risks in % (95% CI)**				**Adjusted incidence rate ratio (95% CI)**	
	First year		Remaining follow-up		After 1 year of follow-up		After 5 years of follow-up		First year	Remaining follow-up
	Alcoholic cirrhosis	Controls	Alcoholic cirrhosis	Controls	Alcoholic cirrhosis	Controls	Alcoholic cirrhosis	Controls		
Total	5.1 (4.1–6.3)	3.4 (3.1–3.8)	3.1 (2.7–3.6)	3.7 (3.6–3.8)	0.38 (0.30–0.47)	0.34 (0.31–0.38)	1.01 (0.88–1.15)	1.64 (1.55–1.72)	1.24 (0.94–1.62)	0.89 (0.76–1.05)
Men	5.4 (4.2–7.0)	4.3 (3.8–4.8)	3.7 (3.1–4.4)	4.6 (4.4–4.7)	0.43 (0.38–0.48)	0.43 (0.38–0.48)	1.08 (0.92–1.27)	2.04 (1.93–2.16)	1.08 (0.79–1.47)	0.85 (0.71–1.02)
Women	4.4 (2.8–6.6)	1.7 (1.3–2.1)	2.1 (1.6–2.8)	2.0 (1.8–2.2)	0.33 (0.22–0.49)	0.16 (0.13–0.21)	0.85 (0.65–1.10)	0.80 (0.71–0.91)	2.13 (1.17–3.87)	1.08 (0.77–1.52)
Age ≤ 49 years	1.6 (0.6–3.2)	0.9 (0.6–1.3)	2.3 (1.7–3.0)	1.6 (1.4–1.8)	0.13 (0.06–0.25)	0.09 (0.06–0.13)	0.70 (0.50–0.97)	0.58 (0.49–0.68)	1.29 (0.40–4.14)	1.48 (1.05–2.09)
Age 50–64 years	4.8 (3.4–6.5)	3.1 (2.7–3.6)	3.2 (2.6–3.9)	3.8 (3.6–4.0)	0.36 (0.27–0.48)	0.32 (0.27–0.36)	0.96 (0.79–1.16)	1.54 (1.44–1.65)	1.29 (0.89–1.91)	0.85 (0.69–1.06)
Age ≥ 65 years	11 (7.7–15)	7.3 (6.2–8.5)	5.0 (3.6–6.8)	7.7 (7.2–8.2)	0.70 (0.50–0.96)	0.72 (0.61–0.84)	1.51 (1.17–1.91)	3.33 (3.08–3.60)	1.21 (0.79–1.84)	0.66 (0.47–0.93)
Compensated	5.0 (3.4–6.7)	3.4 (2.9–4.0)	2.9 (2.3–3.5)	3.9 (3.7–4.1)	0.39 (0.28–0.52)	0.38 (0.29–0.40)	1.03 (0.84–1.25)	1.77 (1.65–1.90)	1.07 (0.71–1.62)	0.80 (0.64–1.00)
Decompensated	5.4 (4.0–7.2)	3.4 (2.9–3.9)	3.4 (2.8–4.1)	3.5 (3.3–0.37)	0.38 (0.28–0.50)	0.34 (0.29–0.39)	0.99 (0.82–1.19)	1.51 (1.41–1.62)	1.32 (0.91–1.90)	1.03 (0.82–1.29)

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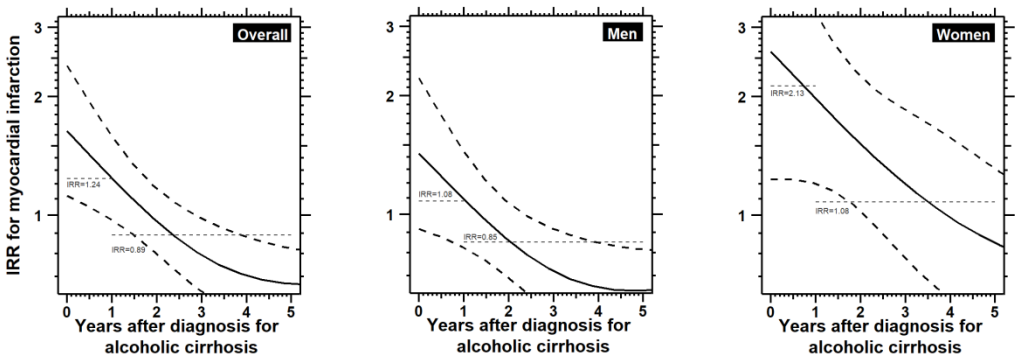

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Figure 1. Adjusted incidence rate ratio (IRR) for myocardial infarction for patients with alcoholic cirrhosis vs. controls according to time since diagnosis for alcoholic cirrhosis, overall (left), men (middle) and women (right). Dashed lines and text in grey represents the IRR for myocardial infarction during the first year after diagnosis for alcoholic cirrrhosis and remaining follow-up. Note the logarithmic y-axes.

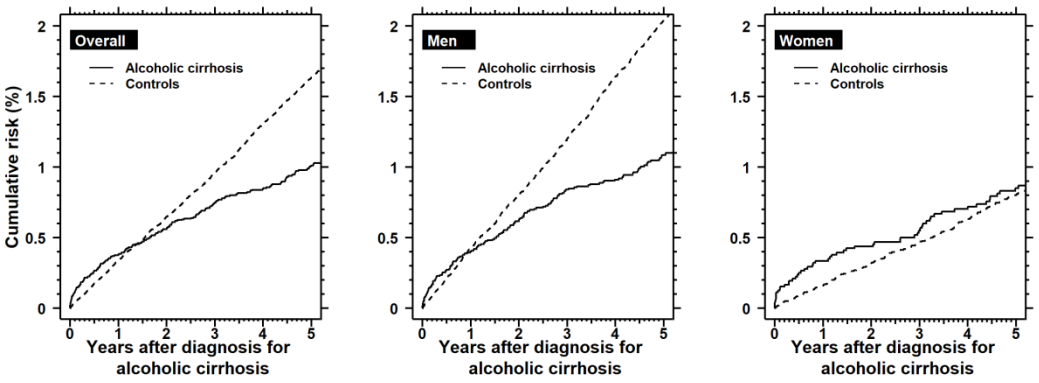

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Figure 2: Cumulative risk of myocardial infarction for patients with alcoholic cirrhosis and controls overall (left), men (middle), and women (right).